PROPOSAL

of the topic approval for the

Degree of Doctor of Philosophy in Life Science

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ABBREVIATIONS

1. hMSCs : Human Mesenchymal Stem Cells
2. ROS : Reactive Oxygen Species
3. MMPs : Matrix Metalloproteinases
4. ECM : Extra Cellular Matrix
5. AGEs : Advanced Glycation End Products
6. FasL : Fas ligand

INTRODUCTION

Cell migration is a vital process in physiological and pathological conditions. The cell effectively synchronizes cellular traction by regulating its cytoskeleton and morphology in accordance to the various mechanical, chemical and biological signals it receives in the milieu. [1,2,3,4] Cell migrates individually or collectively in response to many cues like chemical signals-Chemotaxis[5], substrate stiffness –Mechanotaxis[6,7] and gradient in substrate stiffness that is sensed by dynamic actin in the cytoskeleton-Durotaxis. Faulty migration can lead to multiple life-threatening conditions. So, for a quick and appropriate response to external favourable or repulsive condition, the cell needs to translate external cues and send signals to initiate an internal cascade of reactions. The actomyosin and intermediate filaments are known to play a key role in gap closure mechanism particularly the actomyosin cables which controls the cell crawling by protrusion-extension. The mechanical forces thus generated are transmitted to the neighbouring cells as well as the matrix.[8]

Answers to a few questions like what the cell senses, how the cell senses and its response in migration are partially understood.[2]

Tissue stiffness are shown to regulate homeostasis, development and various pathologies.[9] Human Mesenchymal Stem Cells (hMSCs) have shown to sense the substrate rigidity and accordingly modulate their stiffness as per the space availability.[10] It has been demonstrated that substrate rigidity plays an important role in maintaining stemness in hMSCs *in vitro* by delaying senescence.[11] Thus, cells *in vivo* are guided by multiple signals which induce various biological processes. Nevertheless, the understanding of these processes is limited.

Lack of normal cell migration in pathological conditions like diabetes leads to open soaring wound while, abnormal break away and migration through the bloodstream is seen in cancer metastasis.

Diabetes Mellitus is a chronic, metabolic disease which impairs the body's ability to process glucose due to deficiency in insulin production (Type 1 Diabetes) or losing the capability to utilize it (Type 2 Diabetes). This results in elevating levels of blood glucose whichover a time contributes to serious damage to the heart, blood vessels, eyes, kidneys, nerves.The worldwide prevalence of diabetes has risen from 108 million (4.7%) in 1980 to 422 million (8.5%) in 2014 making it one of the leading cause of global deaths.[12]

The raised blood glucose level creates malfunctions like increase in Reactive Oxygen Species (ROS) and altered Matrix metalloproteinases (MMPs) expression.

ROS is caused by leakage of O_2^- from complex I towards mitochondrial matrix and complex III towards inter membrane space and mitochondrial matrix. Lipid peroxidation and elevated ROS underwrite many vascular complications and also accelerate oxidative damage to DNA and other macromolecules.[13] Mitochondrial ROS production is also seen to induce impaired insulin secretion and insulin resistance which contributes in the development of Type 2 Diabetes.[14]

Matrix metalloproteinases (MMPs) are calcium-dependent zinc-containing endopeptidases. The MMPs contribute in tissue homeostasis and help in degradation of damaged Extra Cellular Matrix (ECM). MMPs are seen to play a vital role in wound healing process right from **inflammatory phase**–by degrading ECM to promote angiogenesis, **proliferation phase** - cell migration, and **remodelling phase** -tightening and remodelling the tissue**.** Disproportionate expression of MMPs is seen to aggravate the chronicity of wound in Diabetic conditions.[15] Advanced Glycation End Products (AGEs) are harmful compounds that are formed when protein or fat combine with sugar in the bloodstream. This process is known as glycation. Recent *in vitro* studies have shown that AGEs induce keratinocyte apoptosis and enhance MMP9 level. Increased expression of Fas ligand (FasL) usually leads to apoptosis. Upregulation of FasL expression by MMP9 results in pro-apoptotic effect on keratinocytesand is seen as one of the cause in delayed diabetic wound healing.[16] Hence probing the cause of imbalance and dysregulation of these proteinases and the impact of external mechanical forces on the wound, may guide in developing MMP directed therapies specific to diabetes.

ECM density and rigidity can influence the cells' response to mechanical cue like stiffness, and also the availability of ligand for cell adhesion. As different organs *in vivo* display diverse ECM and rigidity, it is indispensable to study a cell's response to different stiffnesses and ECM coated surfaces. Studies have shown that substrate rigidity can influence the migration of a cell.[17] Moreover, research has revealed that type of ECM is known to govern

the migration, proliferation and differentiation in myoblast cells. Cells seeded on Collagen IV have shown maximum influence on migration velocity and the proliferation rate when compared with Fibronectin, Laminin and Collagen I.[18] Therefore more investigations regardingthe impact of ECM rigidity and its resultant mechanical response on cell migration will give abetter insight in wound healing impairments in Diabetes.

It is an established fact that wound healing in Diabetes Mellitus is a persistent problem leaving the patient with pain and uncomfortable open wounds. Chronic foot ulcers with infection eventually need lower limb amputation and in certain conditions proves to be fatal. Rigorous and successful study is ongoing to comfort patients with soaring wound by advising oral and topical medications as well as use of scaffolds as regenerative therapy. Different types of wound care products are available like alginates, gauzes, skin sealants, hydrogels, composites, and transparent films. Successful wound management depends on an understanding of the attributes of healing process combined with knowledge of the dynamics of various dressings available. Enhanced understanding of the wound will always increase the probability of wound healing in diabetic conditions.[19]

Mechanobiology is the study of the essential roles of physical factors like force, geometry and matrix elasticity in defining cell and tissue functions, morphology and regeneration as well as human physiology and pathology via the process of mechanotransduction.[20] Biological phenomenon wherein mechanical stress applied to cells are translated into chemical signals that elicit adaptive responses is called mechanotransduction.[21] The process in which cytoskeletal motor proteins – Dyneins, are known to convert chemical energy into mechanical motion, is being deeply studied in the past few decades shedding new light on how these motors "walkthe walk"[22] Cell induces a large number of proteins and protein complexes to sense mechanicalforces and activate signal transduction to communicate , migrate and proliferate during development and disease. Cell crawling, shape change and response to potential pathogens area few examples of coordination between signals and cellular dynamics.[23]Hence it is necessary to probe into the biomechanical signals and biochemical pathways, to identify them and aim atthe probable molecular target.

Scratch Assays are most widely used to interpret the collective cell behaviour and cell migration studies *in vitro*.[24] Some other techniques used for collective cell migration are Trans membrane Assays, Microfluidic Chamber Assays and Cell Exclusion Zone Assays. These tools are popularly used in major drug discovery experiments. Scratch Assays were first utilized as models of wound healing and are considered as cost efficient and easy to perform in research

labs. Cytoskeletal studies such as actin localization can be done using immunostaining, similarly protein and gene study can be done using western blot, while various polymerase chain reaction (PCR) techniques are used to quantify nucleic acid studies. Cell proliferation and tracking can be measured from bright-field images using various types of microscope systems.[25]

Last two centuries have witnessed the escalation of Allopathic system of medicine based on the principle of one drug – one therapy as well as multitarget broad spectrum drugs .[26] The drugs used are largely synthetic and costly and with adverse side effects. Recent occurances of drug resistance of microorganisms to antibiotic and chemical agents, unreasonable use of traditional medicines and incurability of some diseased conditions have urged renewed interest in scientists to study natural products as a potential solution. [27] Medicinal plants have immense healing properties due to the presence of biologically active compounds. Plants have been used as traditional medicines in the Indian subcontinent since antiquity. It is apparent from research that the plants produce secondary metabolites when in stress and these include phytochemicals which have potential medicinal value and constitute an important source of many drugs.[28,29]

It has been demonstrated that phytochemicals are effective against various diseases.[26] Plant parts such as stems, seeds, flowers, leaves, roots, bark have many phytochemicals namely flavonoids, lignans, monoterpenes, cinnamic acids, coumarins, diterpenes, phenylpropanoids, tannins and triterpenes. Studies have depicted that these phytochemicals showed protective effects against many pathological conditions, including oxidative stress (ROS) mediated diseases like diabetes.[30] The ethnobotanical study of medicinal plants has revealed that many tribes used specific plant species to heal cuts and wounds.[31] Thus *in vitro* antoxidant activity of a plant can be evaluated using the free radical scavenging assays, while an alpha-amylase inhibitory assay can be used to determine anti diabetic activity.[32]

Scientists all over the world are promoting a non-animal and human-relevant methodologies in clinical and biomedical research. Centre for Predictive Human Models (CPHMS) has been specially created in India at Atal Incubation Centre-CCMB to serve the purpose.

Therefore, an *invitro* model using hydrogels of different rigidity according to stiffness of organ of study, will provide apt human relevant model and an alternative in promoting non-animal methodologies.[33] Moreover a combination of knowledge of phytochemicals and their influence in mechanotaxis may evolve as a new means of understanding and treating pathological condition like diabetes, which may turn out to be cost effective and with least side effects.

RATIONALE

Cell migrates in response to mechanical, chemical and biological cues which it receives from the surrounding environments. Cell migration plays a central role in physiology, pathology, embryogenesis, immune response, wound healing and cancer metastasis. Any hindrance in healthy cellular migration may have serious consequences. For example in Diabetes Mellitus, a cell's inability to migrate results in delayed or improper re- epithelialization making wound healing process difficult. Due to non-healing or open sore wounds patients not only undergo the trauma of pain and discomfort but also the resulting infection may lead to amputation of limbs (specially foot) or even death. Excess ROS and imbalanced MMPs contribute in enhancing the diabetic wound and delay the process of healing. Various oral medications, topical applications as well as scaffolds are being developedto aid in wound healing and to overcome this trauma but still the problem of open wounds and amputation persists.

Many *in vivo* studies using animal models have been conducted and analysed in case of diabetic condition but very little has been explored regarding the influence of surrounding mechanical microenvironment and the response to the mechanical cues by cells in diabetic condition.

I propose to develop an *in vitro* model that would mimic the diabetic skin in terms of physicochemical environment and cell type used. I envisage that this diabetic wound model will mimic the *in vivo* condition better than the traditional cell cultures done on plastic petri- plates. As a result, this model will not only help us to understand the underlying biology of diabetic wound healing better, but also will reduce the need of conducting animal model studies. Further, using the proposed biomimetic diabetic model, I will be able to decipher the effect of microenvironment stiffness on the ROS activities and regulation of MMPs in diabetic condition. In the other complementary part of this proposed research, I aim to find the combination of phytochemicals that may help in healing the diabetic wounds faster. The knowledge gathered through this project will augment our understanding of traditional wisdoms with modern scientific evidences. If successful, I propose to produce a topical lotion using the phytochemicals to treat non-healing wounds.

AIMS AND OBJECTIVES

Aim:

1) *In vitro* studies of mechanical and biochemical parameters influencing cell migration in healthy and diabetic condition with respect to wound healing using single cell migration assay and collective cell migration - Scratch Assay.
2) Influence of phytochemicals in cell migration and mechanotransduction in cells in both healthy and diabetic condition.

Objectives:

1) To study a diabetic cell model incorporating the *in vivo* condition such as stiffness and ECM with respect to mechanotaxis in wound healing.
2) *In vitro* study regarding the influence of substrate stiffness and ECM on ROS activity during cell migration in healthy and diabetic conditions.
3) To check whether MMPs are up regulated or down regulated in response to external mechanical stimulus using different substrate stiffness in healthy and diabetic conditions.
4) To test the response of phytochemicals extracted from indigenous plants on mechanosensing of the cells in healthy and diabetic condition with respect to
    i) Cell migration pertaining to wound healing.
    ii) ROS activity
    iii) MMP gene expressions

MATERIALS AND METHODS

Materials:

1. Acrylamide
2. Bis-acrylamide–poly linker
3. Sulfo-SANPAH solution **(**sulfosuccinimidyl 6-(4'-azido-2'-nitrophenylamino) hexanoate)
4. Tetramethylethylenediamine (TEMED)
5. Ammonium persulphate (APS)
6. Dulbecco's phosphate-buffered saline
7. 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES)
8. ECM protein
9. Fetal Bovine Serum
10. Dulbecco's Modified Eagle's Medium
11. 6/12-well plate
12. 2 cell lines – healthy and diabetic patient
13. Plant parts (stem, root, leaves, flowers)
14. Soxhlet apparatus
15. Inhibitors - ROS activity and MMP expression
16. Antibodies (Primary and Secondary) against cytoskeletal proteins.
17. Diabetic drugs – Metformin/ silver sulfadiazine

Methods:

1. Polyacrylamide gels of different stiffness coated with the required ECM protein[31].
2. Cultures of cells extracted from healthy individuals and diabetic patients for experimental purpose.
3. Determining cell seeding density for wound healing assay - BrdU Assay and fold change measure.
4. Scratch Assay for wound healing.
5. Immunostaining assay for cytoskeleton network.
6. SDS Page, Western Blot, Chromatography techniques.
7. Soxhlet extraction of phytochemicals
8. MTT assay for cell viability check.
9. Time lapse video microscopy
10. Manual cell tracking and analysis using ImageJ software.

EXPECTED RESULTS

1) Diabetic cell model, mimicking *in vivo* condition, may give a better insight on mechanobiology and microenvironment of a diabetic wound, which will help to deal with chronic problems regarding open wound ailments.

2) This cell model will bridge the gap between *in vitro* petri-plate diabetic studies and *in vivo* animal studies. It will also help promoting a non-animal and human-relevant methodologies in clinical and biomedical research thus will give a novel direction for research in diabetes *in vitro.*

3) The influence of substrate stiffness on ROS activity and MMP profiling under the influence of phytochemicals may be viewed as a potential in repair and regenerative medicine.

4) Putting together, the knowledge gained from this multi-institutional project will help in the field of tissue engineering in making skin scaffolds with right mechanical properties. The scaffold. supplemented with combination of phytochemicals, will helpin treating otherwise non-healing diabetic wounds.

5) This study would lead to develop new cost-effective formulations using phytochemicals.

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8th April, 2021.

Topic Approval

Research and Recognition Committee for the Board of Studies

Life Science

The concerned students, the concerned Research Supervisors and the Head / the Principals of the concerned Research Centres are hereby informed that the applications received from the students for approval of topic of the thesis for **Ph.D.(Science & Technology)** degree course in the subject of **Life Science**, under Section 37(2)(b)(i) of Maharashtra Public Universities 2016, were placed before the **Research and Recognition Committee** for the **Board of Studies** in **Life Science,** at its meeting held on **29th January, 2021,** for its consideration, when the Committee **approved** the outline of the topics submitted by the concerned students.

Sr No	Name of the Candidate	Guiding Teacher	Recommendations
1	Shri. Sylvester Anthony Parkhey	**Dr. Ujawala Jadhav** Associate Professor, Department of Life Science University of Mumbai, Vidyanagari, Kalina, Santacruz (E), **Mumbai – 400 098.**	**Approved**
2	Shri. Sherkhane Pramod Dagadu Annapurna	**Dr. Prasun K. Mukherjee** Scientific Officer 'H', Enviornmental Biotechnology Section, Nuclear Agriculture and Biotechnology D ivision, Bhabha Atomic Research Centre, Trombay, Mumbai – 400 085.	**Approved**
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further, the aforesaid students are hereby allowed to register themselves for **Ph.D. (Science & Technology)** degree course in the subject of **Life Science**, subject to fulfill the UGC conditions on minimum standard and procedure for award of Ph.D. Degree

The registrations of the concerned students are subject to the intake capacity of the Department/College/Institute.

Please note that the students from other than University of Mumbai are required to submit a **Provisional Statement of Eligibility** issued by this University before their admission to the said course in the Department/College/Institution.

Deputy Registrar
RAPC

To,

The concerned students, the concerned Research Supervisors and the Head / Principal / Director of the concerned Research Centre

Copy to the Deputy Registrar, Eligibility and Migration Certificate Section, Dr. Babasaheb Ambedkar Bhavan, Vidyanagari, Santacruz (E), **Mumbai -400 098** forwarded for information.